

WE CLAIM:

- 1 1. A microsphere comprising hyaluronan functionalized with a crosslinker at glucuronic acid sites of
2 the hyaluronan, wherein the derivitized hyaluronan is crosslinked intramolecularly and
3 intermolecularly.
- 1 2. The microsphere of claim 1, wherein the crosslinker is a dihydrazide having the formula:
2
$$\text{H}_2\text{N}-\text{NH}-\text{CO}-\text{A}-\text{CO}-\text{NH}-\text{NH}_2$$

3 wherein A is a substituted hydrocarbyl, unsubstituted hydrocarbyl, substituted heterocarbyl or
4 unsubstituted heterocarbyl moiety, said moiety having one to twenty carbons or heteroatoms.
- 1 3. The microsphere of claim 2, wherein A is a heterocarbyl having heteroatoms selected from the
2 group consisting of nitrogen, oxygen, and sulfur.
- 1 4. The microsphere of claim 2, wherein the carboxyl groups of the glucuronic acid residues have been
2 activated with a carbodiimide.
- 1 5. The microsphere of claim 4, wherein the carbodiimide is 1-ethyl-dimethylaminopropyl
2 carbodiimide.
- 1 6. The microsphere of claim 1, wherein the microsphere is formed by mixing hyaluronan and a
2 dihydrazide in an aqueous solution, adding a substantially non-water miscible liquid and an
3 emulsifying agent to form a water in oil type-emulsion, and lowering the pH of the emulsion.
- 1 7. The microsphere of claim 1, further comprising a component that is incorporated into the
2 microsphere.

- 1 8. A method of making a functionalized hyaluronic acid microsphere comprising mixing hyaluronic
2 acid and a dihydrazide with a crosslinking activator in an aqueous solution, adding a substantially
3 non-water miscible liquid and an emulsifying agent to form an oil in water-type emulsion, and
4 lowering the pH of the emulsion to allow intramolecular and intermolecular crosslinking to occur.
- 1 9. The method of claim 8, wherein the pH of the emulsion is lowered to the range from about pH 7
2 to about pH 4.
- 1 10. The method of claim 8, further comprising dehydrating the microspheres after they have formed.
- 1 11. The method of claim 8, wherein the crosslinking activator is a carbodiimide.
- 1 12. The method of claim 8, wherein at least one molar equivalent of a dihydrazide is added per molar
2 equivalent of glucuronic acid groups on the hyaluronic acid.
- 1 13. The method of claim 8, wherein at least one molar equivalent of a carbodiimide is added per molar
2 equivalent of glucuronic acid groups on the hyaluronic acid.
- 1 14. The method of claim 8, wherein the dihydrazide has the formula:
2
$$\text{H}_2\text{N}-\text{NH}-\text{CO}-\text{A}-\text{CO}-\text{NH}-\text{NH}_2$$

3 wherein A is a substituted hydrocarbyl, unsubstituted hydrocarbyl, substituted heterocarbyl or
4 unsubstituted heterocarbyl moiety, said moiety having one to twenty carbons or heteroatoms.
- 1 15. The method of claim 8, wherein A is a substituted heterocarbyl or an unsubstituted heterocarbyl
2 having heteroatoms selected from the group consisting of nitrogen, oxygen, or sulfur.
- 1 16. A pharmaceutical or cosmetic formulation comprising a pharmacologically effective amount of the
2 microsphere of claim 7 and an acceptable carrier, excipient, or diluent.

- 1 17. A method of administering microspheres to a human or animal comprising administering a
2 pharmacologically effective amount of the pharmaceutical or cosmetic formulation of claim 16.